PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/002190	02.03.2005	25.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D459/00

Applicant
INDENA S.P.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

To section V

The following documents were cited in the search report and were considered for the examination of the present application:

D1: GB 809 913 A (CIBA LIMITED) 4 March 1959,
D2: GB 868 478 A (LES LABORATOIRES FRANCAIS DE CHIMIOTHERAPIE) 17 May 1961,
D3: SAKAI, S.I. OGAWA, M.: "The Chemical Transformation to Deserpidine" HETEROCYCLES, vol. 10, 1978, pages 67-71,
D4: TAMIZ, A.P. ET AL.: "Structure-Activity Relationship for a ...Receptors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 9, 1999, pages 1619-1624.

The present application is directed to the preparation of Deserpidine, a natural product which is to be distinguished from Reserpine by the absence of a methoxy group in position 11. The process is characterized by the demethylation of a methoxy precursor (II) which results in the formation of a hydroxy intermediate (III), which is then reduced. Ring opening of the lactone and esterification results in the formation of the target molecule.

Document D4 deals with a demethylation process in general without mentioning intermediate (III). D1-D3 disclose preparation examples for Deserpidine. None of these documents uses a derivative bearing a methoxy group in position 11 which is then demethylated to a hydroxy intermediate according to formula (III). In view of this difference novelty is acknowledged for claims 1-8. Claims 9-10 are directed to intermediates with a hydroxy or a p-toluenesulfonate group in position 11, which are not anticipated by the prior art. Consequently claims 1-10 are novel (Art. 33(2) PCT).

None of the specified documents suggests the use of an intermediate (III) and thus the requirements of Art. 33(3) PCT are met.

Claim 1 seems not to be in agreement with the description, since the reduction step is accomplished using a 11-p-toluenesulfonate derivative and not a hydroxy intermediate according to formula (III). In view of this difference the requirements of Art. 5 and 6 PCT

are not met. With respect to the transformation of the hydroxy-intermediate to compound (V) no support is provided in the description. If the p-toluensulfonate intermediate is essential for performing the reaction sequence, then it has to be incorporated into claim 1.